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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/643,334	08/22/2000	Edmund F. La Gamma	60435-A/JPW/MMM	9213

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EXAMINER	
BAKER, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	3

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/643,334	LA GAMMA ET AL.	
	Examiner	Art Unit	
	Anne-Marie Baker	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The preliminary amendment filed August 22, 2000 (Paper No. 2) has been entered. Claims 1-64 have been cancelled. Claims 65-79 have been newly added.

Accordingly, Claims 65-79 are pending in the instant application.

Although Applicants refer to "Exhibit A" in the preliminary amendment (p. 5, paragraph 5), the Examiner did not receive Exhibit A, and so has not considered it. If Applicants wish to have Exhibit A on record, Applicants are advised to supply a copy with the response to this Office Action.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

> It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

A preliminary amendment was filed August 22, 2000. The declaration does not specifically refer to the amendment. A newly executed declaration is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759

F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 65-77 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,106,827 (hereinafter referred to as "the patent"). Although the conflicting claims are not identical, they are not patentably distinct from each other because, since new claims 65-74, 76, and 77 are broader than Claims 1-10 of the patent in that they now broadly recite any promoter (or a constitutive promoter or an astrocyte-specific promoter) for regulating expression of the selectable marker gene rather than being limited to the GFAP or RSV promoter, the new claims encompass the invention of the patent. It is noted that the GFAP promoter, as recited in Claims 1-10 of the patent, is an astrocyte-specific promoter, as recited in Claim 77 of the instant application. Thus, new claims 65-74, 76, and 77 read on the patented invention. With regard to Claim 75, it would have been obvious to use the TK promoter instead of the GFAP or RSV promoter to drive expression of the selectable marker gene, particularly given that the specification teaches the use of the TK promoter linked to the neomycin resistance gene in the plasmid pMCINeoPolyA (p. 12, line 14). Thus, Claim 75 of the instant application would have been obvious over Claim 1 of the patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 77, 78, and 79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

With regard to Claim 77, which recites "wherein said regulatable promoter comprises an astrocyte-specific promoter," the specification fails to provide an enabling disclosure for this embodiment because the specification does not teach astrocyte-specific promoters that are regulatable and such promoters were not known in the art at the time of the invention. For example, although the GFAP promoter was known in the art to be an astrocyte-specific promoter, there was no evidence that it was a **regulatable** promoter. Neither the specification nor the prior art teach how to regulate astrocyte-specific promoters. Thus, one of skill in the art would have been required to engage in undue experimentation in order to isolate or create regulatable astrocyte-specific promoters.

Claim 78 is directed to a method of expressing DNA encoding a biologically active molecule in a subject. The method involves taking an astrocyte comprising a DNA encoding a biologically active molecule, transplanting the astrocyte into a subject, and expressing the biologically active molecule in the astrocyte in the subject. Thus, Claim 78 is directed to *ex vivo* gene therapy. Claim 79 is directed to a genetically modified astrocyte comprising a third DNA encoding a poison pill. The specification clearly teaches at pages 25-26 that the only use for a genetically modified astrocyte comprising a gene encoding is poison pill is for transplantation purposes, such that if the activity of the transplanted cells is no longer desired, the transplanted cells can be selectively killed by administration of an appropriate compound (such as gancyclovir in the case of the use of the thymidine kinase gene).

The specification fails to teach how to use the claimed method and composition for the only asserted utility (*i.e.*, *ex vivo* gene therapy). The specification teaches that the only use for the claimed method (Claim 78) and the composition of Claim 79 is for *ex vivo* gene therapy. However, the specification fails to provide an enabling disclosure for gene therapy.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of neural tissue or other cells into the central nervous system (CNS) are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect, but the specification does not adequately teach how to use the claimed method and/or composition to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue. The specification does not offer any guidance as to how the claimed method and/or composition could be used therapeutically for the treatment of any disorder. No working examples demonstrate a therapeutic effect for the claimed method of transplantation. The specification provides general teachings only, but does not provide specific guidance for treating a pathological condition. The specification fails to provide any guidance relating to the number of cells to inject, the site of injection, and the extent of cellular persistence required and attainable in practice, to provide any therapeutic benefit for the treatment of any disorder.

The claims are directed to methods of *ex vivo* gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification fails to teach any method for transferring a gene encoding a

biologically active molecule into an astrocyte and subsequently transplanting the astrocyte and expressing the gene *in vivo* at a level sufficient to produce a therapeutic effect in a diseased animal. The specification does not provide any guidance as to the level of gene expression required, the number of transduced cells needed, the site of transplantation, when, where, or for how long the gene should be expressed, the frequency of administration of the gene therapy vector (i.e., the cells) required, or in some embodiments, the intended target tissue, for treatment of any pathological condition in an animal. The specification also lacks any working examples showing that the contemplated genetically modified astrocyte, once transplanted to the appropriate site, would be expressed at a level sufficient to provide adequate product to effect the desired therapy in an immunocompetent animal. At the time the application was filed, the art of administering any type of genetic expression vector, including genetically modified cells, to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed method and composition for *ex vivo* gene therapy. Thus, absent any showing that the

claimed method and composition can be used in gene therapy applications to produce the intended therapeutic effect in an animal, such as a human, the claims directed to gene therapy are not enabled by the disclosure.

Given the lack of specific guidance in the specification, the broad scope of the claims, and the lack of working examples directed to producing a therapeutic effect upon transplantation, one of skill in the art would have been required to engage in undue experimentation to practice the claimed method or use the claimed composition.

The specification is drawn to the use of the present invention for gene therapy. Thus, while the claims do not specifically recite that the invention is "for gene therapy," the utility of the invention is clearly, as stated in the specification, directed to gene therapy. For example, Claim 79 is drawn to a genetically modified astrocyte comprising a third DNA encoding a poison pill. Although the phrase "for gene therapy" has been deleted from the claim, the use of a genetically modified astrocyte comprising a poison pill gene as set forth in the specification is for therapeutic transplantation.

In the parent application, Applicant argues that the claims are no longer directed to methods "for gene therapy" using astrocytes, but rather to methods for expressing a biologically active molecule in astrocytes (p. 11 of Paper No. 25 of Application Serial No. 08/862,438). However, the invention is clearly drawn to gene therapy, in particular therapeutic transplantation of the genetically modified astrocytes (see e.g., p. 1, lines 10-22; p. 4, lines 14-16; p. 18, lines 25-31 of the Specification). No other use for the claimed method or the genetically modified astrocyte of Claim 79 is contemplated in the disclosure of the invention. As set forth in the Office Action mailed 12/9/97 (Paper No. 23 of Application Serial No. 08/862,438), for the reasons summarized below, undue experimentation would have been required by one

skilled in the art at the time the application was filed to use the claimed invention for the purpose intended. A number of experiments described in the specification and the prior art point to the level of unpredictability for the therapeutic transplantation of genetically modified astrocytes. Expression of the transgene and induced expression of the transgene are unpredictable for a number of reasons. First, experiments show that expression in a damaged region of the brain is significantly less than in an undamaged region. The level of ppENK promoter-driven expression of the reporter gene was diminished in astrocytes transplanted to the lesioned striata of rats relative to the level of expression in astrocytes implanted at an undamaged site (p. 24, lines 24-26). Second, the dopaminergic agonist apomorphine further reduced ppENK promoter-driven CAT activity *in vivo* (p. 24, lines 24-35), whereas *in vitro* experiments had demonstrated induced expression of the gene under this promoter (p. 21, lines 4-31). Third, the prior art taught that the level of expression of genes in astrocytes varies with the location of the astrocytes in the brain (Shinoda et al., pp. 415-416). Thus, the use of the genetically modified astrocytes for gene expression-dependent therapy is rendered an unpredictable and uncertain practice because the specification does not teach how to achieve therapeutically effective levels of transgene expression in a damaged region of the brain, the *in vitro* data cannot be used to predict effects *in vivo* as evidenced by the opposite effects of apomorphine produced *in vivo* and *in vitro*, and the promoter activity varies depending on the location of the astrocyte within the brain as taught by Shinoda et al. In addition, the astrocytes can migrate up to 8 mm from the site of transplantation, thereby making the ultimate placement of the cells somewhat imprecise (Blakemore et al., 1991).

The specification does not provide any guidance as to the level of transgene expression required, the number of transformed cells needed, the site of transplantation, or the method of implantation, for treatment of any pathologic condition. The prior art teaches that animal models of human

neurodegenerative diseases are not expected to respond to transplantation in the same way as humans suffering from the disease because the models do not accurately duplicate the physiological and biochemical parameters of the disease state. For example, many models are produced by acute physical damage to the brain, whereas the causative agent of the neurodegenerative disease is chronic, continuing to persist after the transplant (see Lindvall, p. 376).

Given the high level of unpredictability in the art of transfecting and transplanting primary astrocytes into a recipient animal's brain to successfully obtain transgene expression, and in recognition of the additional unpredictability of applying to humans therapeutic regimens developed in animal models of human disease, one skilled in the art would not consider the disclosed exemplification to be predictive of the successful operation of the claimed invention wherein primary astrocytes transfected with a gene expression construct are transplanted into the brain of an animal or human to produce therapeutic expression of a biologically active molecule, such as tyrosine hydroxylase.

In the parent appliction, Applicant argues that by deletion of the phrase "for gene therapy," ribozymes and anti-sense RNA are enabled for use in the transfected astrocytes, but the specification fails to provide an enabling disclosure for how to make or use any such ribozymes or anti-sense RNA, and as argued above the only use for the claimed method is for therapeutic transplantation.

In the parent application, Applicant argues that the specification does in fact provide an enabling disclosure for the use of the poison pill. However, it is maintained that the specification fails to teach how to use a poison pill such as described. The specification discusses only what is intended to be done with the poison pill and how it is intended to work, but does not actually describe and teach how to do what is intended.

It is noted that Applicant has not offered any particular arguments that address how one would have practiced the claimed invention to achieve any therapeutic effect upon transplantation of a genetically modified astrocyte.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 65-79 are indefinite in their recitation of "said promoter" at line 13 of Claim 65 because the term has ambiguous antecedent basis. There are two promoters recited in the claim; there is one promoter that drives expression of the selectable marker gene and another promoter that drives expression of the gene encoding the biologically active molecule. Thus, it is unclear to which promoter "said promoter" is intended to refer.

Claims 65-79 are indefinite in their recitation of "said DNA" at line 9 of the Claim 65 because the term has ambiguous antecedent basis. The claim refers to "a first DNA encoding a selectable marker and a second DNA encoding a biologically active molecule." Thus, it is unclear to which DNA "said DNA" is intended to refer.

Claim 76 is indefinite in its recitation of "wherein said regulatable promoter comprises a constitutive promoter" because a constitutive promoter is not regulatable. See p. 457 of Elseth et al. which states "[o]f course, not all genes are subject to regulation. Constitutive gene are continuously expressed." Furthermore, it is unclear how a regulatable promoter can **comprise** a constitutive promoter, given that a promoter cannot **comprise** anything other than a promoter.

Claim 77 is indefinite in its recitation of "wherein said regulatable promoter comprises an astrocyte-specific promoter" because it is unclear how a regulatable promoter can **comprise** an astrocyte-specific promoter, given that a promoter cannot **comprise** anything other than a promoter. Use of claim language reciting "wherein said regulatable promoter is an astrocyte-specific promoter" is suggested.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Crouch, acting SPE, can be reached on (703) 308-1126. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Kay Pinkney, whose telephone number is (703) 305-3553.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER